RESEARCH REVIEW JOURNALS
Volume-04
Issue-01
January -2019

ISSN: 2455-3085 (Online)
RESEARCH REVIEW International Journal of Multidisciplinary
www.rrjournals.com [UGC Listed Journal]

# Systematic Review of the Efficacy of Metformin in Diabetes Mellitus Patients – Meta Analysis

*[1]J. Vijay Anto & [2]Lilly George

[1]*Ph.D. Research Scholar, Department of Statistics, St. Joseph's College (Autonomous), Tiruchirappalli, TamilNadu (India)*
[2]*Assistant Professor & Head, Department of Statistics, St. Joseph's College (Autonomous), Tiruchirappalli, TamilNadu (India)*

**ARTICLE DETAILS**

**Article History**
*Published Online:* 10 January 2019

**Keywords**
DM, Efficacy, Forest plot, Funnel plot, Metformin, RCT

***Corresponding Author**
*Email: antovijayja[at]gmail.com*

**ABSTRACT**

Diabetes Mellitus (DM) is a progressive and non-communicable disease. Around 9 percent of the people suffer due to this disease in all over the world. There are several interventions available to treat the disease; one among them is Metformin. It is the choice of most of the clinical practitioners for treating DM.

In this article, systematic review methodology has been adopted to assess the effect of the intervention 'Metformin'. Systematic review finds solution for a research question through 'n' number of research articles which are already done by others. Several related articles are extracted from the internet and they are validated (whether good article or not) by five point Jadad scale. Good quality articles' data are further analysed through Meta analysis. Thus, 5 articles are taken for the systematic review.

Risk ratios are calculated in each selected articles and they are compared with one another. Random effect model has been applied to accommodate variation between studies in Meta analysis. Meta Analysis such as forest plot and funnel plot are used to validate the efficacy of the Metformin in DM patients. R-programming language is utilized to carry out the work. The results are displayed in tables and figures.

## 1. Introduction

Ageing is the one of the risk factors for many diseases; one among them is diabetes mellitus (DM). DM is the most common disease for the human beings. It is commonly categorized into two (i) Type I diabetes and (ii) Type II diabetes. Diabetes is the cause for the adverse events like, kidney impairment, blindness, nerve problems, loss of limbs and so on. Insulin is the hormone that carries glucose from the bloodstream and serves the same to each and every cell in the body. Type I diabetes is categorized as people who have insufficient insulin level. Due to the inadequate level of insulin, glucose content will enhance in the blood. Hence, type I diabetes patients need to be taken insulin injection, in order to control the hyperglycemia in the body.

People with type II diabetes have adequate level of insulin. However, their bodies' cells do not use the insulin properly. Thus, blood glucose levels are increased in the blood stream. Type II diabetes is the most common diabetes. Because most of the people are affected by type II diabetes compared with type I diabetes. Metformin is the one of the effective and safe drug which deals the type II diabetes[1]. It is a Food and Drug Administration (FDA) approved prevention and treatment drug for type II diabetes in the US since 1990[2]. Asian countries especially India have high prevalence rate of Impaired Glucose Tolerance (IGT). The IGT (Prediabetes) have high prone to exhibit diabetes. Therefore, adequate level of prevention is needed in these countries.

This paper tries to evaluate the effectiveness of Metformin in the diabetes risk patients. The evaluation is made by systematic review approach. i.e., to find a solution for a research question through the studies which are already done by others.

## 2. Methodology

Good quality research articles need to be included in the systematic review. Since, if the primary studies are biased, the finding which is coming from the primary studies is also being biased. The quality of the methodology in the primary studies can be validated through five point Jadad scale.

Jadad scale is used to assess the clinical trials of published research. Usually, the Jadad score ranges from 0 to 5. The Jadad scale includes totally seven items. Among them, five items have positive score and two items have negative score[3] . The items are given below:

i. The trial is randomized control trial [+1]
ii. Randomization is done by random number table/Computerized [+1]
iii. The study design is double blind [+1]
iv. The study includes identical placebo / active placebo / dummy placebo [+1]
v. The description of dropout from the study [+1]
vi. Study stated as randomization. However the treatment allotted based on non-randomization [-1]
vii. The study stated as double blind. But inappropriate methodology has been opted out. [-1]

The studies which have more than 3 score are considered as good articles. They are included in the systematic review process. Thus, five articles have been selected and they are further analyzed through systematic review approach.

Risk ratio has been calculated for ascertaining the difference between the experimental group and control group. The ratios have been displayed in the forest plots. The publication bias has been assessed by funnel plot.

RRIJM 2015, All Rights Reserved

### 3. Parent Articles

Ramachandran et al (2006)[4] conducted a research regarding effect of metformin along with lifestyle modifications to prevent the diabetes among the IGT subjects. In this research, the authors applied the randomized controlled trial. The target population of study individuals is those who have IGT on the basis of WHO criteria. This is the prospective study over the period of 3 years. In this study, one group of study individuals had standard health care advice (Control group) while another group of study individuals had Metformin (Experimental group). After completion of the study period, totally 133 were in control group and 128 were in Metformin group. The incidence rate of diabetes was 55% (n=73) in the control group while the incidence rate was 40.5% (n=52) in the Metformin group.

Diabetes prevention program research group (2002)[5] conducted a prospective study over the period of 2.8 years. The research group included the subjects who have the high risk of type II diabetes. In the study, 1073 subjects had taken Metformin while 1082 subjects had placebo treatment. At the end of 2.8 years study period, the incidence rate of DM was 7.8% (n=84) in the Metformin group while it was around 11% (n=119) in placebo group.

Travor J. Orchard et al (2005)[6] conducted a prospective study over the period of 3.2 years. Through this study, the authors find out the effect of lifestyle intervention and metformin therapy among the IGT subjects. Totally 490 participants received placebo treatment and 503 participants received metformin. After the 3.2 years follow-up period, 260 participants had the metabolic syndrome in the placebo treatment group while 236 participants had the same in the metformin group.

Jose A. Luchshinger et al (2017)[7] conducted a diabetes prevention program outcomes study with the assistance of Metformin and lifestyle intervention. In this study, those who have high risk of IGT were included. Totally, 776 subjects received Metformin while 755 received placebo treatment. Among the Metformin group patients, 391 had the risk of diabetes while 437 members had the risk of diabetes in the placebo group.

Diabetes prevention program research group (2005)[8] conducted a RCT trial in order to prevent the type II diabetes among the high risk people. In the design, the people are randomly assigned 587 in Metformin group and 582 in placebo group. At the end of the study, 7% had the risk of diabetes in Metformin group while 12% had the risk of diabetes in placebo group.

### 4. Meta Analysis

The R-software presented both statistical models (i) Fixed effect model and (ii) random effect model. However, the studies are conducted in different locations and different countries' people. Hence, the effect could be varying based on the samples. Therefore, random effect model is more appropriate than fixed effect model[9] . In addition, heterogeneity between the studies is represented by Tau-squared and I-squared values. The heterogeneity statistics I2 is very close to 50%. It also reveals that heterogeneity presented in the studies. Hence, random effect model is the best fit in the data. Also, the statistical significance value (p>0.05) of Q statistic connotes that the included studies share the common effect size.

***Table 1: Number of subjects developed type II diabetes in the metformin group and placebo group***

| Study | No. of Subjects in Metformin | No. of diabetes in Metformin | No. of subjects in Placebo | No. of diabetes in Placebo |
|---|---|---|---|---|
| Ramachandran et al (2006) | 128 | 52 | 133 | 73 |
| DPPRG (2002) | 1073 | 84 | 1082 | 119 |
| Travor et al (2005) | 503 | 236 | 490 | 260 |
| Jose A Luchsinger et al (2017) | 776 | 391 | 755 | 437 |
| DPPRG (2005) | 587 | 41 | 582 | 70 |

***Table 2: Statistical fixed effect model and random effect model***

| | RR | 95% CI | Z-value | p-value |
|---|---|---|---|---|
| Fixed effect model | 0.8241 | [0.7684, 0.8838] | -5.42 | <0.0001 |
| Random effect model | 0.8061 | [0.7185, 0.9044] | -3.67 | <0.0002 |

#### *4.1 Quantifying Heterogeneity*

tau^2 = 0.0075; H = 1.40 [1.00; 2.32]; I^2 = 49.1% [0.0%; 81.4%]

#### *4.2 Test of heterogeneity*

Q=7.86; df= 4; p-value=0.0967

RRIJM 2015, All Rights Reserved 

### *4.3 Forest Plot*

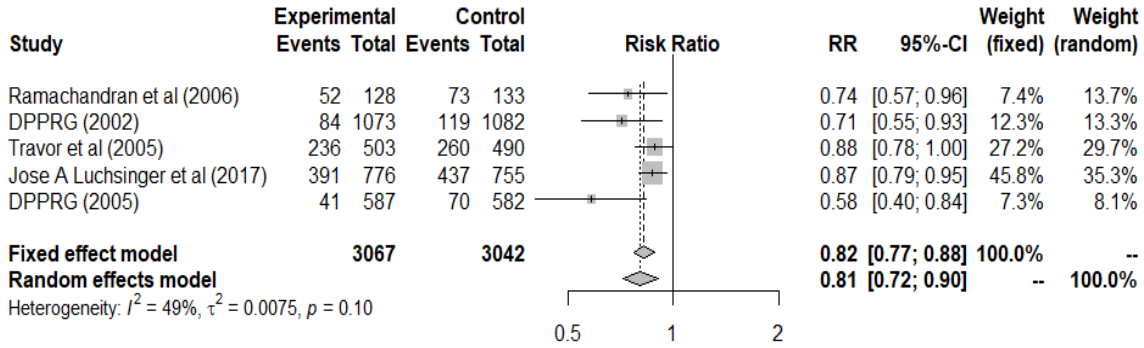


*Figure 1: Forest plot*

The forest plot clearly depicts that the risk ratios of cumulative effect of the metformin and the individual study effect of metformin. The point estimation of risk ratios of individual studies are less than 1, which clearly depicts that Metformin significantly reduces the risk of diabetes compared with placebo/control group. However, one study [Travor et al (2005)] has the risk ratio with 95% confidence interval from 0.78 to 1.00. This study reveals that Metformin group IGT patients and control group IGT patients do not have the same level of risk to have diabetes. However, this difference is not statistically significant.

When considered the random effects model, the cumulative risk ratio is 0.81, which indicates that Metformin group individuals have less likely to get diabetes compared with the control group. In addition, the 95% confidence interval are varies from 0.72 to 0.90. This interval does not include the value 1, which indicates that IGT patients who consume Metformin have less prone to affect diabetes compared with IGT patients who do not consume. This difference is statistically significant.

### *4.4 Funnel Plot*

Publication bias has significant negative effect in clinical trials. Majority of the clinical trials are accepted for publication, only when they produce the significant positive result. Hence, we may not know about the actual effect of the drug like adverse effect until and unless insignificant result studies are published. Therefore, we should know whether any publication bias existed in our research.

Publication bias has been assessed through funnel plot in this study. The X-axis represents the effect size of the metformin while the Y-axis represents the standard error. The dots inside the funnel plot indicate that the risk ratios across the standard error. They scattered symmetrically in both tails[9]. It could be concluded that there is no publication bias existed in the review of our Metformin efficacy study.

## 5. Conclusion

Random effect model has been adopted in the meta analysis as there is some heterogeneity presented in the collected articles. This clearly specifies that meta analytical approach is good. The cumulative risk ratio connotes that Metformin significantly reduces to have the risk of diabetes compared with placebo/conventional intervention. Hence, Metformin prevents to develop diabetes from IGT. The funnel plot also indicates that there is no publication bias existed in the review of Metformin efficacy research. Therefore, our research is valid.

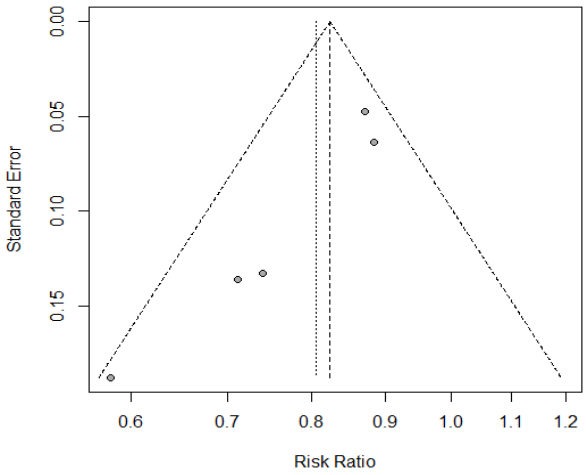


*Figure 2: Funnel Plot*

***Acknowledgement***

We would like to thank Dr. C. Deiveegan, Dr. Sudharsan and Dr. Saravanan, Assistant professors of Community Medicine,Velammal Medical College Hospital & Research Institute, Madurai, for their valuable feedback to improve this article.

## References

1. https://clinicaltrials.gov/ct2/show/NCT02432287
2. https://clinicaltrials.gov/ct2/show/NCT03467763
3. Halpern, S. H., and M. J. Douglas. "Appendix: Jadad scale for reporting randomized controlled trials." Evidence-based

Obstetric Anesthesia. Oxford, UK: Blackwell Publishing Ltd (2005): 237-238.

4. Ramachandran, A., Snehalatha, C., Mary, S., Mukesh, B., Bhaskar, A.D. and Vijay, V., 2006. The Indian Diabetes Prevention Programme shows that lifestyle modification and metformin prevent type 2 diabetes in Asian Indian subjects with impaired glucose tolerance (IDPP-1). Diabetologia, 49(2), pp.289-297.
5. Knowler, William C., et al. "Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin." The New England journal of medicine 346.6 (2002): 393-403.
6. Orchard, Trevor J., et al. "The effect of metformin and intensive lifestyle intervention on the metabolic syndrome: the Diabetes Prevention Program randomized trial." Annals of internal medicine 142.8 (2005): 611-619
7. Luchsinger, José A., et al. "Metformin, lifestyle intervention, and cognition in the Diabetes Prevention Program Outcomes Study." Diabetes care (2017): dc162376.
8. American Diabetes Association. "Prevention of type 2 diabetes with troglitazone in the Diabetes Prevention Program." Diabetes 54.4 (2005): 1150-1156.
9. Antonisamy, B., Premkumar, P.S. and Christopher, S., 2017. Principles and Practice of Biostatistics-E-book. Elsevier Health Sciences

**Appendix: R-programming language for Meta Analysis**

```
library(meta)
setwd("location of the data")
dat<-read.csv("dataname.csv", header=TRUE, sep=",")
ls()
summary(dat)
str(dat)
fix(dat)
RRmeta<-metabin(event.e, n.e, event.c, n.c,studlab=study, sm="RR", data=dat)
View(dat)
ls()
RRmeta
summary(RRmeta)
forest(RRmeta, comb.r=T, comb.f=T)
metainf(RRmeta)
q()
funnel(RRmeta, comb.r=T, comb.f=T)
```

RRIJM 2015, All Rights Reserved 